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Disease-a-Month

Shock in Infectious Diseases

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Jackson A. Smith—PSYCHOACTIVE DRUGS

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Shock in Infectious Diseases

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TABLE OF CONTENTS

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SHOCK remains a dread complication of certain infections despite antibiotics. The continued prevalence of shock in infectious diseases (infectious shock) can be partly attributed to antibiotic-resistant organisms; but the failure of antibiotics to prevent shock even from susceptible bacteria emphasizes the role of nonviable bacterial products, or toxins, in its pathogenesis. Host factors, such as age and blood loss, also influence the development of shock during infection. Because the recognition and treatment of infectious shock involve an understanding of the underlying mechanisms, the present discussion is based on an analysis of the complex interaction between these microbial and host factors.

NATURE OF SHOCK

Whatever the initiating cause of shock, the end result is a constellation of metabolic derangements which, at a point commonly referred to as irreversible shock, does not permit recovery even if the cause is completely removed. The mediating factor is in-

adequate perfusion of vital organs, resulting in failure of their function. Shock may be defined as failure of the microcirculation in tissues (1). Although the lethal outcome finally depends on widespread organ failure, the shock syndrome is characterized by clinical signs that reflect the operation of compensatory mechanisms involved in the redistribution of blood to vital organs that require uninterrupted perfusion. Thus the classic picture of shock includes tachycardia and cutaneous vasoconstriction—a homeostatic "comeback"—as well as mental torpor—evidence of circulatory failure.

Shock in infectious diseases, however, is variable in its manifestations and often deviates from the classic picture because of the peculiar effects of each microorganism or its toxin. Such deviations from classic shock take many forms, including the hot, dry and flushed appearance often evident early in septicemia, especially that due to gram-negative organisms; the unusual mental alertness that characterizes patients with clostridial septicemia; and the bradycardia sometimes seen in myocarditis. In looking for a criterion common to all forms of shock, clinicians have come to rely on blood pressure measurement both as a diagnostic tool and as an index of therapeutic success. The treatment of blood pressure rather than of shock has been criticized (2, 3) on the basis that vasoconstrictor drugs further deprive organs of blood. For diagnostic purposes, however, it may be safely assumed that significant hypotension is a manifestation of actual or impending circulatory failure.

Although most of the reports dealing with the problem of shock in infections have concerned themselves with cases of demonstrated bacteremia (4-8) and especially those due to gram-negative bacilli, intravascular bacterial multiplication is not a prerequisite for vascular collapse, since dead gram-negative bacilli and their endotoxins have induced hypotension in man. Moreover, the occurrence of shock in infections due to gram-positive organisms, which liberate a variety of exotoxins in localized infections without bacteremia, as in gas gangrene, further illustrates that shock may be a purely toxic rather than an infectious phenomenon. At the other extreme, direct invasion of organs with destruction of vital tissues or obstruction of blood

flow may result indirectly in circulatory failure on a purely mechanical basis.

PATHOGENESIS OF INFECTIOUS SHOCK

Circulatory failure, in its strictest sense, is defined at the capillary level. The capillaries, however, form only one link in the circulatory chain; dysfunction at any point in the circulation may lead to inadequate flow through the capillaries. Return of venous blood to the heart, cardiac output and functional integrity of the arteriolar tree are the broad areas in which disturbances may lead to peripheral circulatory failure. For this reason, the classification shown in the table is applied to shock occurring in infections.

These factors may be aggravated by anoxia in severe infections of the respiratory tract (influenza) or the central nervous system (poliomyelitis). Prolonged anoxia causes capillary atony (11) and damage to the myocardium. The effect of anoxia is vividly illustrated in cases in which hypotension occurs in conjunction with poor oxygenation and blood pressure is restored by the administration of oxygen (12, 13).

MECHANISMS OF SHOCK IN INDIVIDUAL INFECTIONS

1. *Gram-negative bacilli; Meningococcus; Cholera vibrio.*— Infections due to these bacteria are characterized by the elaboration and dissemination of endotoxins that are capable of widespread damage to the circulation. Although in its most typical form endotoxic shock is usually associated with bacteremia, it is well known from experimental work in animals (14, 15) and from experience with sterile typhoid vaccine in human subjects (16, 17) that the same effects can result from circulating endotoxin in the absence of viable bacteria. Sudden hypotension during the transfusion of blood contaminated with cold-growing gram-negative organisms (18) is due to toxin already present in the transfused blood and may occur without demonstrable bacteremia (19). Endotoxic shock may also occur during the antibiotic treatment of gram-negative infections; within hours after

CLASSIFICATION OF SHOCK DUE TO INFECTION

MECHANISM OF SHOCK	DISEASES IN WHICH MECHANISM IS OPERATIVE
I. Impaired venous return	
A. Reduced blood volume	
1. Fluid loss due to capillary damage	Gas gangrene; anthrax; hemorrhagic fever
2. Loss of water and electrolytes	
a) Severe diarrhea	Cholera; staphylococcal enteritis
b) Adrenal insufficiency	Tuberculosis; histoplasmosis
c) Salt-losing pyelonephritis (9)	
d) Peritonitis	
B. Normal blood volume	
1. Peripheral pooling	Gram-negative bacillary infections; meningococcemia; staphylococcal septicemia; gas gangrene; influenza; rickettsial diseases; systemic candidiasis
II. Impaired cardiac function	
A. Myocardial failure	
1. Myocarditis	Diphtheria; influenza; other virus infections; rickettsial infections; trichinosis; toxoplasmosis; Chagas' disease
2. Myocardial infarction	Coronary embolism in subacute bacterial endocarditis
B. Cardiac tamponade	
1. Pericardial effusion	Pericarditis due to tuberculosis, actinomycosis
2. Hemopericardium	Ventricular rupture, as in tuberculous myocarditis (10)
C. Mechanical outflow obstruction	
1. Intraventricular blockage	Rupture of echinococcus cyst into ventricle
2. Pulmonary embolism	Myocarditis with mural thrombosis
III. Disturbance of arteriolar tone	
Destruction of vasomotor center	Bulbar poliomyelitis

the beginning of treatment the patient undergoes a typical pyrogenic reaction associated with vascular collapse (20), presumably due to the release into the circulation of large amounts of endotoxin from destroyed bacteria.

The details of the hemodynamic alterations due to endotoxin are incompletely understood. Although in all animals studied arterial hypotension is a prominent feature, the events taking place in different parts of the circulatory system show a good deal of species variation, so that only broad generalizations are possible regarding the effects of endotoxin in man. Both the arterial and the venous side of the circulation are thought to be affected. Animal studies have shown alternating vasoconstriction and vasodilatation in small vessels (21–23). In human beings there is initial arteriolar constriction, evident in a transitory rise in blood pressure without a rise in cardiac output. This phase is followed, in mild cases, by one of warmth and flushing, indicating arteriolar dilatation. In severer cases, the latter phase gradually gives way to one of full-blown shock with peripheral vasoconstriction, pallor and coldness of the skin. The details of these reactions have been described by various investigators (6, 24–26). Measurements of cardiac output have given variable results, being normal in some series (27, 28) but low in the majority of patients in other series (29). From the point of view of localizing the site of action of the endotoxin, among the more significant findings are (*1*) reduced right atrial pressure (29) and (*2*) normal blood volume (30, 31). These findings clearly rule out both heart failure and loss of circulatory blood volume as causes of shock and make it likely that the mechanism is diminished venous return due to peripheral pooling. It has been inferred from autopsy data on patients dying in bacteremic shock that pooling occurs in the liver and intestines (32, 33); on the other hand, similar changes have not consistently been present in fatal cases of shock due to contaminated transfusions (19, 34). Controlled observations after injection of endotoxin into many species of animals have shown a spectrum ranging from marked splanchnic pooling and mild pulmonary edema in the dog to no splanchnic congestion but severe pulmonary edema in the cat.

Although the effect of endotoxin is evidently vascular, the mechanism of action on the vessel wall has been only partly

elucidated. It is apparent that direct contact of endotoxin with blood vessels is without effect (23, 25). On the other hand, changes were produced in the isolated perfused dog lung only when the perfusing fluid was whole blood or cell-rich plasma (36). The nature of the mediator is still controversial, since a number of vasoactive substances have been found in increased concentrations in the blood of animals subjected to endotoxic shock. Among these are catecholamines (37), histamine (38, 39) and serotonin (40). It has been shown in rabbits that unusually small amounts of epinephrine will cause skin necrosis after pretreatment with endotoxin (41). Progressive changes in vascular reactivity to epinephrine were also noted (42), with initial hyperreactivity followed by vasodilatation; in the latter phase, relaxation of arterioles exceeded that of venules, so that the net effect was capillary congestion. Furthermore, both adrenocortical steroids and adrenergic blocking agents aborted these reactions. To what extent this sequence of events explains peripheral pooling in man remains open to question, especially since attempts to demonstrate altered epinephrine reactivity in dogs have met with negative results (43, 44). Dogs, however, show increased vascular reactivity to histamine (39). Recent studies (45, 46) showing increased decarboxylation of histidine to histamine during endotoxic shock support the claim for the importance of histamine release.

An interesting sidelight on the problem of endotoxic shock has come from investigations into the role of intestinal bacteria in the syndrome of irreversible hemorrhagic shock (49, 50). The finding of an endotoxin-like substance in the plasma of irreversibly shocked animals, the protection of animals against irreversible shock by the prior administration of nonabsorbable antibiotics, the demonstration of cross-tolerance between shock due to hemorrhage and that due to endotoxin, and the abolition of both types of tolerance by reticuloendothelial blockade (51) have suggested that bacterial endotoxin absorbed through an abnormally permeable intestinal mucosa contributes to the irreversibility of hemorrhagic shock.

The pathogenesis of shock in meningococcemia probably does not differ significantly from that in infections with gram-negative bacilli. As a result of the original reports of Waterhouse (52)

and Friderichsen (53) describing adrenal hemorrhage in fatal cases of meningococcemia, the impression was created that peripheral vascular collapse and death in such cases resulted from adrenal insufficiency. Subsequent autopsies in fatal cases of the so-called Waterhouse-Friderichsen syndrome, however, failed to show adrenal hemorrhage with any consistency (54, 55), and it is now thought that the effect of meningococcal toxin resembles that of gram-negative bacillary toxins in causing widespread vascular dysfunction. Adrenal hemorrhage, when it occurs, is presumably a local manifestation of vascular damage and is not in itself a cause of peripheral vascular collapse. The suggestion has also been made (56) that cutaneous and adrenal hemorrhages in this disorder represent the local Shwartzman phenomenon. In bacterial shock from various infecting organisms the plasma levels and half-life of hydrocortisone were increased and the patients displayed an increased response to ACTH (57); meningococcal shock was not, however, represented in this series. Experimental observations on the effect of meningococcal toxin in dogs (58) revealed decreased cardiac output due to decreased venous return, while total peripheral resistance was not significantly changed.

Cholera vibrios also produce an endotoxin, but its role in human disease is uncertain. The organism is noninvasive and acts chiefly to cause edema, hyperemia and inflammation of the intestinal tract. This direct effect on the intestine results in losses of fluids and electrolytes of sufficient extent to produce vascular collapse. Unlike patients in shock from endotoxemia, those with cholera show marked hemoconcentration; in the latter the hematocrit may exceed 60, plasma proteins 12 Gm./100 ml., serum sodium 160–170 mEq./L. and serum osmolarity 400 mOsm./L. (59). On the other hand, there is no doubt that cholera endotoxin is potentially capable of systemic damage. Intraperitoneal injection of killed vibrios leads to peritoneal exudation, edema of the intestines and myocardium, and hemoconcentration, while parallel experiments with killed typhoid bacilli cause vascular collapse without hemoconcentration (60). In vitro studies have yielded a vibrio extract that increased the flow across rabbit and guinea pig intestines (61) and an enzyme that caused desquamation of guinea pig intestinal mucosa (62). Increased capillary

permeability in an isolated loop of small intestine upon instillation of cholera vibrios has also been noted in vivo (63). If cholera endotoxin plays a part in human infection (64), its importance is overshadowed by the effects of dehydration.

2. *Clostridium.*—In human disease, the most important of the numerous clostridial toxins are the lecithinases of Cl. perfringens, Cl. septicum, Cl. oedematiens, Cl. sporogenes, Cl. bifermentans and Cl. histolyticum, and the neurotoxins of Cl. tetani and Cl. botulinum. Tetanus and botulinum toxins are not associated with shock syndromes, and will not be considered here. The other species are referred to collectively as the gas-gangrene organisms because of their common occurrence, singly or in various combinations, in gas gangrene (65). Severe cases of this disease are associated with marked systemic disturbances terminating in vascular collapse and death without bacteremia. It is generally accepted that the exotoxins are the responsible agents. To what extent their distribution throughout the body is a requisite, however, is not clear. The lecithinases of pathogenic clostridia are powerful hemolysins, and the hemolytic potency of Cl. perfringens is greater than the lethal potency (66); yet intravascular hemolysis is not a feature of fatal gas gangrene, although it is characteristic of clostridial septicemia. Furthermore, attempts to isolate clostridial toxin from blood, wound exudates or infected tissue extracts in clinical or experimental clostridial myositis have not been uniformly successful (67). The failure of large amounts of circulating antitoxin to influence the course of the disease and the prompt improvement after surgical removal of infected tissues (68) have led to the belief that the toxin acts locally to form an intermediate toxin that cannot be neutralized by clostridial antitoxin. The tissue damage that would accompany production of such an intermediate toxin would also contribute to the pathogenesis of circulatory collapse. Direct observation of the skin of guinea pigs has disclosed increased capillary permeability upon the administration of the alpha toxin, a lecithinase of Cl. perfringens, Cl. oedematiens and Cl. septicum (69). Experimental intramuscular infection in dogs (70, 71) results in local congestion, edema, capillary hemorrhage and muscle necrosis. Findings in human clostridial myositis are similar. The extensive exudation of fluid leads to hypovolemic

circulatory effects which have been compared to those of severe burns (72). Hypovolemia is not the only circulatory disturbance, however, because a marked fall in cardiac output has been observed (71) with only slight fall in blood volume in Cl. oedematiens infection in dogs. Furthermore, intravenous infection of these animals leads to marked hemodynamic changes after a latent period of about one hour. At autopsy, there are widespread changes, including edema and hemorrhage in the lungs, congestion of the liver, congestion and submucosal hemorrhage in the intestine and hemorrhage in the adrenals as well as the heart. It is likely, therefore, that peripheral pooling as well as extravasation takes place.

3. *Staphylococcus.*—The toxic properties of staphylococci were vividly illustrated in the Bundaberg disaster of 1928 (73), when children were fatally inoculated with pathogenic staphylococci during immunization against diphtheria with contaminated materials. The infected children suffered a fulminating course characterized by gastrointestinal disturbances, sphincter incontinence, disturbance of consciousness, fever, tachycardia, and shock—a syndrome that has been well documented by Kleiger and Blair (74). The rapid evolution of this illness speaks strongly for a toxic rather than an infectious etiology, and the properties of staphylococcus exotoxin support the concept. The vascular reaction (75–77) in dogs poisoned with staphylococcus toxin produces hepatic engorgement, increased portal pressure and decreased vena caval pressure with a small heart. Both mesenteric arteries and veins undergo spasm; the kidneys become congested as a result of venospasm and fail to fill with India ink. The blood vessels also undergo medial necrosis. Staphylococcus alpha toxin, like gram-negative endotoxin, enhances sensitivity to epinephrine in experimental animals (78). The total picture, then, is one of peripheral congestion and pooling with resultant decrease in venous return and in cardiac output.

Another staphylococcal product, enterotoxin, has also been considered to be a cause of vascular collapse. Food poisoning due to enterotoxigenic staphylococci is rarely severe, although in occasional outbreaks some patients have presented a picture compatible with vascular collapse (79). The clinical picture of food poisoning with shock has been reproduced in human volun-

teers by feeding culture filtrates from enterotoxigenic staphylococci (80), but the possibility exists that alpha toxin was also present in these materials.

Staphylococci have been isolated frequently from the stools of patients with pseudomembranous enterocolitis, a necrotizing lesion of the gastrointestinal tract usually leading to vascular collapse and death. Although diarrhea is a prominent feature of this disease, the rapid course suggests an intoxication rather than mere dehydration. Although staphylococcus alpha toxin is thought by some to be the responsible agent, others have pointed to the high incidence of enterotoxigenic strains among the staphylococci isolated from pseudomembranous enterocolitis—30 of 30 cases in one series (81). The possibility exists, therefore, that enterotoxin may be instrumental in the etiology of this syndrome (82).

4. *Streptococcus.*—Severe streptococcal infections occasionally are attended by circulatory collapse (83–85), but its mechanism is not clear. One line of investigation has led to the discovery of a streptococcus endotoxin (86–88). Although much less potent, it shares the properties of gram-negative bacillary endotoxin in its capacity to cause fever, neutropenia and death in animals; to prepare or provoke the Shwartzman reaction; and to elicit a nonspecific resistance, or tolerance, for various types of group A streptococcus toxins. It exhibits no consistent cross-tolerance for gram-negative endotoxins and differs from them chemically (86). Other experiments have shown that an exotoxin, streptolysin O, has striking cardiotoxic properties. Isolated heart muscle from guinea pigs, rabbits and rats loses its contractile power on perfusion with streptolysin O (89), while intravenous injection of this substance in rabbits almost immediately produces cardiac arrhythmias that usually prove fatal (90). While it is possible that either of these toxins is operative in human shock due to streptococcal infections, their role remains to be established.

5. *Diphtheria.*—The circulatory collapse that often precedes death in diphtheria appears to be both peripheral and cardiogenic. The temporary benefit often achieved by the intravenous administration of fluids to patients with a failing circulation indicates that the problem is one of effective hypovolemia and sec-

ondary to peripheral pooling. Such effects have been ascribed to changes in the peripheral vasomotor mechanism (91) or to loss of vasomotor control (92). Unfortunately, detailed studies of the peripheral circulation have not been reported, and descriptions of pathologic studies of diphtheritic neuropathy have dealt almost exclusively with somatic motor and sensory nerves (93).

A more easily recognized cause of shock is that seen in myocarditis. This complication may be clinically evident in only 10–20% of cases despite electrocardiographic evidence of myocarditis in 65–80%. Vascular collapse frequently accompanies progressive heart failure (94), but shock is sometimes precipitated by a sudden arrhythmia, a common clinical manifestation of myocarditis in diphtheria.

The exact mode of action of diphtheria toxin is unknown, but it is believed to involve a disturbance of cellular respiration through interference with the cytochrome system (95). This is compatible with the widespread degenerative lesions formed in various organs of animals experimentally poisoned with diphtheria toxin.

6. *Other bacterial infections.*—Pneumococcal pneumonia, even in the absence of severe anoxia or direct cardiac involvement, is sometimes associated with shock (83). Shock may also occur in the course of pneumococcal meningitis (96). Because no toxin has been isolated from pneumococci that can reproduce such effects in animals, the mechanism of the reaction is obscure. The vascular collapse is probably of peripheral origin. Impaired vasomotor tone, with decreased contractility of skin vessels in response to stroking and to epinephrine, has been demonstrated in patients with pneumococcal pneumonia (97).

Peripheral circulatory collapse has also been reported in the course of pneumonia and bacteremia due to Hemophilus influenzae (98). The shock was attributed to hemophilus endotoxin.

In these, as in other bacterial infections in which shock may occur, the relative importance of bacterial products, host factors and hypersensitivity phenomena remains to be elucidated.

7. *Influenza.*—Circulatory collapse in influenza (99, 100) usually occurs in severe cases of pneumonia. Because influenzal pneumonia is characterized by anoxia, frequently by secondary staphylococcal infection and sometimes by myocarditis, the de-

velopment of shock is theoretically traceable to staphylococcus toxin, anoxia, cardiac failure or the action of influenza virus, together or alone. Scattered observations indicate that influenza virus itself has a direct action on the circulatory system. Thus, changes in digital blood flow (101) have been reported even in the absence of circulatory failure; influenza virus is adsorbed on the endothelium of hepatic blood vessels (102); and intravenous injection of influenza virus produces rapid hypotension (103, 104), apparently due to direct action on the myocardium.

8. *Poliomyelitis.*—A wide variety of cardiovascular disturbances is seen in poliomyelitis (13), including hypotension and shock. Shock can come about in a number of ways, its mode of development depending on the distribution of lesions in the nervous system and heart and on the presence or absence of secondary complications. The following factors may be responsible for the development of shock:

a) Vasomotor center lesions. It is not generally agreed that hypotension can be attributed to medullary lesions. Although damage to the reticular substance in the medulla has been found in poliomyelitis patients dying in vascular collapse (105), the same lesions have also been described in patients dying in shock from other causes (106).

b) Myocarditis. This lesion has been reported frequently in poliomyelitis since it was recognized 20 years ago (107). Its incidence varies from 25 to 85% in fatal cases. Patients with recognized myocarditis frequently suffer also from respiratory embarrassment or bulbar lesions, so that it is extremely difficult to ascribe circulatory changes to cardiac involvement alone.

c) Hypoxia. This may result from hypoventilation, pulmonary edema, atelectasis or accumulated secretions. Although its role in shock has been debated, hypoxia seems to be a critical factor when hypotension and anoxia develop simultaneously. In this circumstance, the hypotension can be reversed by the administration of oxygen (12).

d) Artificial respiration. Neither intermittent positive-pressure breathing nor negative-pressure (tank) breathing properly simulates the normal respiratory cycle, and the dynamics of blood flow in and out of the thorax can be seriously altered (108). Venous return, in particular, may be hampered. Nevertheless,

artificial respiration alone will not cause hypotension unless the balance of compensatory mechanics is further upset by complications such as pneumonia. Hypotension occurring in patients with pneumonia has been reversed simply by removing them from the tank respirator (13). After the pneumonia was successfully treated, they tolerated the tank without fall in blood pressure.

e) Secondary bacterial infection. Patients with already impaired circulatory dynamics are particularly vulnerable to the cardiovascular effects of bacterial infection. This is especially important in view of their increased susceptibility to pulmonary and urinary tract infection.

9. *Hemorrhagic fever.*—The etiology of this disease is unknown but thought to be viral (109). Shock occurs during defervescence, from the fourth to sixth day of illness (110), and is characterized by hypovolemia, hemoconcentration and increased peripheral resistance. Widespread soft tissue congestion, edema and hemorrhage (111, 112) accompany the oligemic shock produced by extravasation of fluid through damaged capillaries. Occasionally patients tolerate progressive reduction in blood volume for as long as 24 hours and then suddenly develop shock without further loss of fluid; thus it seems that vascular tone is suddenly lost. By direct serial observation of nailfold capillaries, both functional impairment and a hemorrhagic diathesis have been established (113).

10. *Rickettsial diseases.*—Shock in epidemic typhus, Rocky Mountain spotted fever and scrub typhus is probably related to diffuse vascular damage (114). Capillary permeability increases in mice and rats inoculated intravenously with rickettsial suspensions and is accompanied by edema and hemoconcentration. These effects are considered to be toxic, rather than invasive, because they begin within 20 minutes after injection. The applicability of such observations to human patients is open to question, however, since hemoconcentration and decreased plasma volume are not generally part of the syndrome in man (115) and the vascular damage becomes most evident several days after the infection is established. Tissue edema is not a characteristic autopsy finding, as would be expected if there had been extensive exudation during life. Although fluid loss

has been claimed to be the cause of the vascular collapse (116), the possibility of functional damage to the capillaries as a cause has not been ruled out. The latter mechanism would be equally consistent with the finding of a heart of normal size and normal or low venous pressure in the presence of arterial hypotension in typhus (116).

While vascular damage is the outstanding feature in Rocky Mountain spotted fever and epidemic typhus, it is less prominent in scrub typhus (117). Instead, the latter produces a higher incidence of myocardial involvement.

11. *Fungi.*—Although shock may occur terminally in disseminated fungus infections, not enough information is available to elucidate its mechanism. A recent report stresses the occurrence of shock in disseminated candidiasis (118). Myocardial abscesses were present, but it is doubtful that cardiac dysfunction can be ascribed to them since such abscesses occasionally are seen as purely incidental findings in most other fungus infections (119–123). The common pathogenic fungi are known to elaborate endotoxins which are lethal for mice (124) and pyrogenic for rabbits (125). Although shock does not occur in the experimental animal from a single exposure to fungus endotoxin, repeated inoculations of various dead fungi induce a state of hypersensitivity that leads to sudden death on subsequent exposure to the same fungus.

12. *Protozoa and other parasites.*—The trypanosome of Chagas' disease characteristically invades the myocardium and produces a true invasive myocarditis. Hypotension has been reported during the acute stage of this disease (126, 127) and may be related to myocardial injury. Likewise, acute toxoplasma myocarditis may be complicated by hypotension (128).

Another parasite capable of invading the myocardium is echinococcus. Vascular collapse and sudden death may occur with rupture of a myocardial hydatid cyst, by a number of mechanisms: *(1)* intracardiac blockage by the cyst contents; *(2)* acute cor pulmonale due to pulmonary embolism (cyst contents); *(3)* hemopericardium and cardiac tamponade due to epicardial rupture; *(4)* anaphylactic reaction to discharged contents of the cyst (129).

Trichinous myocarditis occurs during the phase of migration

of the larvae and may lead to death. Hypotension frequently occurs during its course (130). Careful human autopsy studies, including digestion of myocardial tissue, as well as experimental infection in rats (131), indicate that invasion of the myocardium by larvae does take place but that they do not encyst there. The possibility of a hypersensitivity reaction also exists, as illustrated by the presence of a predominantly eosinophilic exudate in the myocardium of a patient at a time when eosinophils were not prominent in the cellular reaction surrounding encysting larvae in skeletal muscle (132); unfortunately, the presence of larvae in the myocardium was not ruled out in this case.

CLINICAL MANIFESTATIONS OF INFECTIOUS SHOCK

Circulatory collapse may interrupt the course of a benign infection or herald the onset of a severe one. Because immediate recognition of the infectious etiology often means the difference between life and death, this section will describe the typical settings of infectious shock and present illustrative case-reports.

Shock in Gram-Negative Infections

The most widely appreciated form of infectious shock is that attributed to the endotoxin of gram-negative bacteria. It may occur in such conditions as typhoid fever and other salmonella septicemias, shigellosis and the transfusion of contaminated blood; but in modern hospital practice the most common setting is the instrumentation of a patient with a urinary tract infection. Bacteremia may occur after cystoscopy or without a recognizable immediate precipitating cause in a patient with an indwelling catheter. Classically, the patient suddenly has shaking chills and an abrupt rise in temperature, often to 104 F. He may be apprehensive and look acutely ill, but there is no new localizing symptom. Hypotension sets in shortly thereafter. The skin may be warm, dry and flushed at first, a phase when the prognosis is good; later the typical clammy, cold skin with peripheral cyanosis appears. Suppression of the urinary output and increased catabolism from fever may lead to uremia and acidosis in an

alarmingly short time. The following case illustrates the fatal character of such a complication.

Gram-negative bacteremia and shock following cystoscopy.—A 68-year-old man was being studied for the possibility of disseminated tuberculosis. Previous retrograde pyelograms had failed to show a renal shadow on the right and renal tuberculosis was suspected. Cystoscopy was attempted but not completed because of pain and difficulty in passing the instrument. About five hours later he experienced a shaking chill, temperature rose to 103.4 F. and pulse rate to 130, while the blood pressure fell to 80/60. Within 15 minutes he was in shock, with blood pressure 40/0. Therapy was started with levarterenol, hydrocortisone, chloramphenicol and saline. For the next 48 hours the patient remained in shock with blood pressure that required the continuous use of vasoconstrictors. During this period he was oliguric; serum potassium rose to 6.0 mEq./L. and carbon dioxide-combining power fell to 18 mEq./L. Finally he became refractory to the vasoconstrictors and died. Pseudomonas aeruginosa was cultured from blood and urine.

This case is especially interesting in that pseudomonas is almost never implicated in spontaneous urinary infections and almost invariably introduced from without.

Obstetric shock.—A variant of the usual clinical syndrome produced by bacteremia is seen in obstetrics and results from pelvic trauma. The incidence of gram-negative genital infections increases during prolonged labor and following abortion. Rupture of the membranes before labor provides a portal of entry for ascending vaginal infection. The clinical picture is characteristic. A chill is followed by fever, with few symptoms of toxicity at first and no signs of shock. Shock ensues 8–36 hours after the chill. In obstetric practice, in which shock is usually associated with hemorrhage, bacteremic shock may go unnoticed unless vital signs and urine output are closely followed. A typical case, described by Studdiford and Douglas (28), was that of a 23-year-old woman who aborted in her fifth month of pregnancy following abdominal trauma. On hospitalization she was febrile but normotensive. Despite prompt antibiotic therapy she went into shock several hours later. Vasoconstrictor therapy was necessary to maintain the blood pressure level, but following hysterectomy she recovered. Escherichia coli was cultured from the blood as well as from the placenta. The authors emphasized the importance of removal of the infected uterine contents, either

spontaneously or surgically, because of their poor accessibility to antibiotics.

Cellulitis and bacteremia due to E. coli.—An unusual focus of infection by a gram-negative organism is illustrated by the case of a patient who died in shock following cellulitis and septicemia due to E. coli. The location of the cellulitis suggested that the origin was in the urinary tract.

A 48-year-old man without previous symptoms became feverish and vomited while noting pain in the suprapubic area and thighs; later in the day he had chills. Urinary function was normal. On hospitalization, temperature was 103.8 F., pulse rate 124, blood pressure 60/0. His skin was described as "lividly" red. There were extreme lower abdominal tenderness and an area of cellulitis over the lower abdomen and upper thigh. White blood cell count was 7,900 with relative neutropenia (41%), hemoglobin 13.4 Gm., serum carbon dioxide-combining power 17.8 mEq./L., blood urea nitrogen 19 mg. per 100 ml. Following a traumatic catheterization, bloody urine was obtained which showed no organisms on direct smear; no evidence of subcutaneous extravasation was found. Despite vigorous treatment with saline, penicillin, tetracycline, streptomycin, chloramphenicol, erythromycin, levarterenol and hydrocortisone, the patient died in shock. A heavy growth of E. coli was isolated from the blood and subcutaneous tissue.

Transfusion of contaminated blood.—Chills, fever and shock occurring suddenly during the infusion of blood may be due to bacterial contamination. A typical reaction occurred in a patient described by Braude and co-workers (4). A 28-year-old man with anemia due to Hodgkin's disease experienced chills, nausea and vomiting after receiving 50 ml. of blood within 40 minutes; subsequently he went into shock and temperature rose to 104 F. Smear of the bottled blood revealed numerous gram-negative rods in each oil-immersion field. Despite acute renal failure, the patient responded to antibiotics, levarterenol and cortisone. Blood cultures from both the bottle and the patient revealed innumerable colonies of E. freundii.

Gram-negative septicemia of obscure origin.—Rarely, septicemia occurs in the absence of a detectable focus of infection. Although an intestinal portal of entry seemed likely in the following patient, the nature of the lesion was not elucidated.

A 56-year-old man noted left lower abdominal pain, vomiting and yellow, loose stools, followed within a day by chills. Temperature on

hospitalization was 101 F. and blood pressure 80/60. He was flushed, but no localizing signs were found. He was treated with penicillin, streptomycin, tetracycline and levarterenol and made an uneventful recovery. Innumerable colonies of E. coli grew in the pour plates from the blood, but their site of origin was not established.

Gram-negative septicemia in the debilitated patient.—Although gram-negative bacilli seldom enter the blood stream from portals other than the perineum and pelvis, an important exception is in the debilitated patient, especially one with disturbed immune mechanisms. In such a patient the low concentration of gram-negative bacilli often present in the pharynx can cause pneumonia, which not uncommonly is the terminal event in his life. In the following case both Staph. aureus and E. coli were involved in the pulmonary infection, but the latter alone was recovered from the blood and probably accounted for the shock.

A 43-year-old man, known to have had lymphosarcoma for three years, developed arthralgias and a positive lupus erythematosus preparation while taking prednisone. The dose of prednisone was doubled and two weeks later he was hospitalized with a perforated peptic ulcer. Despite his generally poor condition, surgery was deemed advisable and closure of the perforation was undertaken. During the postoperative period he remained febrile, with temperature ranging between 102 and 105 F. Blood pressure persisted in the range of 100–110/80, compared to 142/70 on admission. Physical examination revealed signs compatible with right lower lobe pneumonia. Treatment with tetracycline and hydrocortisone caused no clinical response. Continuous tachycardia in the range of 130–150 was refractory to digitalis. On the fourth postoperative day the blood pressure fell to 84/44 and was not significantly elevated by levarterenol. Penicillin, streptomycin and erythromycin were added to the regimen, but shock continued and the patient died on the morning of the fifth postoperative day. Sputum culture contained Staph. aureus and E. coli. The latter was also cultured from the blood. During the postoperative period, despite daily urine output of approximately 1,000 ml., the blood urea nitrogen rose from 26 to 148 mg./100 ml., carbon dioxide-combining power fell from 26 to 21 mEq./L., but electrolytes remained normal. Autopsy was not performed.

Shock in meningococcemia.—Although the mechanism of shock due to meningococcemia is very similar to that in infections due to gram-negative bacilli, there are important differ-

ences. The infection is typically one of children and young adults previously in good health, and the route of infection is respiratory. Although the typical meningococcal infection begins with respiratory symptoms and progresses to meningitis, either or both of these phases may be lacking. The syndrome of marked toxicity, fever and purpura with varying degrees of vascular collapse, however, appearing suddenly in an otherwise healthy young person is so characteristic that the diagnosis readily suggests itself; furthermore, the organism can be seen in smears taken from cutaneous petechiae, or from the spinal fluid if meningitis is present. Shock may be present early in the disease but often develops later, even while treatment for the infection is already well under way. The variability of the course of meningococcemia is illustrated by two patients described by Kanter and co-workers (133). One of them, a 21-year-old soldier, became acutely ill with headache, chills, fever, vomiting and bloody diarrhea. Temperature was 101.6 F., pulse rate 90, blood pressure 110/60. Both purpura and meningitis were present; the organism was recognized in spinal fluid smear and cultured from the blood. Despite prompt therapy with large doses of penicillin and sulfadiazine, shock ensued, with blood pressure 50/30. Aqueous adrenal extract and lipoadrenal extract failed to raise the blood pressure, which, however, promptly rose to 100/50 in response to levarterenol. The patient finally recovered. In this case, the absence of any prodrome and the seemingly specific effect of sympathomimetics are noteworthy.

The second patient, an 18-year-old soldier with an upper respiratory infection of four days' duration, was admitted with temperature 103 F. and blood pressure 120/60. The only physical findings were related to pharyngitis. Neurologic and spinal fluid examinations were normal. Ten hours later, he was covered by a petechial rash and several ecchymoses. Therapy was begun at this point with sulfisoxazole, but eight hours later he went into shock with temperature 99.2 F., pulse rate 120, blood pressure 60/40. Levarterenol brought the blood pressure to 90/50, and it was held there with the addition of steroids. Thirty-six hours after therapy was begun, oliguria and congestive heart failure were noted, the blood urea nitrogen being 70 mg./100 ml. With digitalis and careful fluid administration the patient finally re-

covered. This case illustrates meningococcemia without meningitis. It also points up two complications of shock and fluid therapy, namely, renal failure and congestive heart failure; the consequent necessity for restriction of fluid intake may be a serious problem in the occasional case in which levarterenol is effective when other sympathomimetics are not.

Shock in hemophilus infection.—Infection by this organism is rare in adults because of lasting immunity acquired in childhood. Lowering of host resistance, as in chronic alcoholism, may result in the establishment of such infection. A case of hemophilus pneumonia was described by Kaplan and Braude (98) in a 52-year-old alcoholic itinerant. When first seen after four days' illness, temperature was 102 F., pulse rate 120, blood pressure 130/70, and there were findings suggestive of right upper lobe pneumonia. Hemophilus influenzae was cultured from the sputum and two blood specimens. Although therapy with penicillin and tetracycline was promptly begun, shock occurred 10 hours later that did not respond to oxygen but was reversed by levarterenol. Recovery thereafter was uneventful.

Shock in Clostridial Infections

Clostridial infection occurs in both localized and generalized forms. The organism either is introduced from without (*gas gangrene*) or originates in the intestinal tract (*clostridial enteritis*) or the vagina (*postabortal clostridial septicemia*). Although the infection takes various forms, vascular collapse is common to all. The anaerobic requirements for local clostridial proliferation can be met in tissues devitalized either by trauma, as in severe injuries (65) or induced abortion (134), or by ischemia, as in arteriosclerosis.

Gas gangrene complicating arterial insufficiency.—This form of clostridial shock is illustrated by the following case:

An 81-year-old man underwent an above-knee amputation of the left leg following femoral artery thrombosis. The course was smooth until 40 hours postoperatively, when temperature rose to 101.4 F. and he went into shock. Edema and crepitation of the thigh were noted and large gram-positive rods were seen on a smear of the aspirated fluid. The hip was disarticulated and treatment with antibiotics begun. Despite

this, levarterenol was necessary for eight hours following the second amputation to maintain blood pressure. After this, recovery was uneventful.

A portal of entry little emphasized in the American literature is needle puncture. Epinephrine is frequently involved since its injection site is surrounded by an area of relative ischemia. Such a case was described by Koons and Boyden (135) in a 63-year-old man who received epinephrine in oil in the buttock. Within 14 hours he was severely ill with temperature 106 F., and a few hours later he was in shock. Death occurred within 24 hours. A large area of gluteal and thigh muscle was involved in a necrotizing, gas-forming myositis from which Cl. perfringens was cultured. It is likely that the organisms originated in the patient's intestine, since bowel flora, including clostridia, is often found on the perianal skin (136).

In *clostridial septicemia,* bacteria and their products contaminate the blood stream more extensively than in gas gangrene (134, 137). A classic form of clostridial septicemia sometimes follows septic abortion. Clostridia are carried into the uterus where, following death of the fetus, anaerobic conditions permit their growth. The vascular placental bed allows ready access to the maternal blood stream, and within a day chills and fever signal the onset of a septicemia distinguished by: (*1*) unusual mental alertness considering the severity of the illness; (*2*) evidence of intravascular hemolysis—hemoglobinuria, hemoglobinemia and often jaundice; (*3*) shock. Renal failure is a common complication, resulting no doubt from shock and hemolysis. The diagnosis is based on the finding of abundant clostridia on Gram stain of a cervical smear, subsequently confirmed by culture. As with other clostridial infections, definitive therapy must include removal of the devitalized uterine contents. The rapid course of this infection is well illustrated by the following case:

Postabortal clostridial septicemia.—A 23-year-old woman developed abdominal cramps and fever two days after abortion by means of a rubber catheter. She was in shock on hospitalization and died before adequate therapy could be instituted. Antemortem blood culture showed a heavy growth of Cl. perfringens. Bacteroides and Str. faecalis were present in smaller numbers; the organisms were also seen on a capillary blood smear.

Intravascular hemolysis was well illustrated in some of the

patients described by Douglas and co-workers (134). One, a 24-year-old woman, attempted abortion in the third month of pregnancy with a Lysol douche and instrumentation. Six hours later she was in shock, with blood pressure 88/62. Hemoglobin was 7.0 Gm. and the urine was wine-colored. Icterus developed while she was in the hospital. Blood culture yielded Cl. perfringens, and morphologically similar organisms were seen in placental fragments.

In rare cases, clostridia may gain direct access to the blood stream from their normal habitat in the bowel, but only when injury to the intestinal barrier is combined with abnormalities of the circulating leukocytes. In leukemia, for example, clostridial septicemia has been noted in patients suffering from leukemic infiltration of the intestinal mucosa (138). Patients with malignancy involving the bowel have had clostridial septicemia following treatment with triethylenethiophosphoramide (139). In some patients with blood dyscrasias, the intestinal barrier may be broken by causes other than malignant infiltration. This is illustrated by the following case:

Clostridial shock in aplastic anemia.—A 54-year-old woman, who had had aplastic anemia for eight months, entered the hospital because repeated transfusions, corticosteroids and androgen preparations had failed to control an increasing tendency to bleed. On admission, temperature was 99.2 F., blood pressure 156/98. Except for many mucocutaneous hemorrhages and signs of hypercorticism, findings on examination were normal. White cell count was 850, with 38% neutrophils, 56% lymphocytes and 6% monocytes. Hemoglobin was 11 Gm. and platelets 16,000. On the second hospital day she complained of nausea and abdominal pain, temperature rose to 101.8 F., and she had a loose, bloody bowel movement. She was treated with kanamycin but failed to improve; four hours later she vomited and her temperature reached 104 F. In the next six hours abdominal pain became progressively severe, vomiting and bloody diarrhea continued, and the patient went into shock, with blood pressure 50/20. Neither levarterenol nor whole blood restored circulation. She died 14 hours after the first temperature elevation. Autopsy revealed gangrene of the cecum and gas-filled spaces in nearly all viscera. Cultures of blood ante mortem and of the viscera at autopsy yielded a heavy growth of Cl. septicum.

A rarely reported clostridial infection associated with shock is *necrotizing enteritis.* This entity was recognized in outbreaks in

in northern Germany in 1946–48 (140) but has been mentioned only in isolated reports since (141, 142). The possible relation of Cl. perfringens to pseudomembranous enterocolitis has received little attention in the American literature, where the staphylococcus has been implicated in the vast majority of cases of supposed bacterial origin. In most series, however, there is an appreciable number of cultures which are staphylococcus-negative. In 16 cases of necrotizing enterocolitis recently reported from Great Britain (143), eight of 11 cultures were positive for Cl. perfringens, and only four of these also contained coagulase-positive staphylococci.

Shock in Staphylococcal Infections

Shock in staphylococcal septicemia has been reported by a number of authors (144–146) since the observation of fatal circulatory collapse in victims of the Bundaberg disaster (73). Staphylococcal septicemia takes one of two characteristic forms. The first is a fulminating disease characterized by tachycardia, abdominal pain, diarrhea, incontinence, meningismus, coma and delirium (74). Shock frequently occurs and death follows rapidly. Autopsy reveals remarkably few metastatic abscesses and the pathogenesis is thought to be an intoxication by the exotoxin (147). Septicemia is found in young patients; this possibly represents a lack of immunity due to insufficient previous exposure. It is illustrated by the following case.

Shock in staphylococcal septicemia.—A 22-year-old man in the convalescent stage of poliomyelitis developed fever thought to be due to epididymitis; this partially subsided. He then had a sudden elevation of temperature and went into shock. Blood culture revealed coagulase-positive staphylococcus. The infection responded well to neomycin and erythromycin.

The second type of staphylococcal septicemia, more common among older patients, is slower in evolution and is associated with the formation of disseminated foci or abscesses, pneumonia, meningitis or endocarditis. Shock and death do not supervene until relatively late in the disease. A skin infection is a common portal of entry. The staphylococcus does not establish itself easily in the normal lung except in infancy, but staphylococcal pneu-

monia frequently occurs following viral pneumonia—especially influenza—or in a chronically diseased lung. The following case illustrates an infection of several days' duration in an old man whose respiratory tree had probably become vulnerable as a result of a viral infection.

Shock in staphylococcal pneumonia.—A 69-year-old man had an upper respiratory infection for two weeks and then began to feel feverish. A few days later his cough became worse and he received penicillin and chloramphenicol from his physician on three successive days. His cough then became productive of pus and blood and he was hospitalized. Temperature was 103.2 F., pulse rate 130, blood pressure 110/70, respirations 36. He seemed acutely ill and dehydrated. Lips and nailbeds were moderately cyanotic. There was evidence of pneumonia in the left lower and right upper lobes. The remainder of the examination was unremarkable. White blood cell count was 9,100, with 78% neutrophils and mild shift to the left. Hemoglobin was 14.0 Gm. Large clusters of gram-positive cocci were seen on sputum smear and were shown by culture to be Staph. aureus. Therapy with penicillin, oxygen, fluids and bronchodilators was begun, but the patient's condition became worse and four hours later the temperature was 105.4 F. After 12 hours, erythromycin, chloramphenicol and hydrocortisone were added. Approximately 17 hours after admission the blood pressure fell to 90/60 and subsequently to 80/0. Despite the addition of levarterenol and the performance of an emergency tracheostomy, deterioration continued and the patient died less than 24 hours after admission. Autopsy was not performed. The pneumonia did not appear to be severe enough to result in anoxia on the basis of respiratory insufficiency.

Staphylococcal enteritis takes one of two forms. The first, so-called staphylococcal food poisoning, is not an infection in the true sense, in that enterotoxin preformed in inadequately refrigerated food is responsible for the symptoms. Fluid loss through diarrhea and vomiting may require intravenous replacement, but dehydration to the point of shock is almost unknown. Antibiotic therapy is unnecessary. The second form of enteritis in which the staphylococcus has been implicated appears to be a true infection due to staphylococcus. In the majority of cases it follows abdominal surgery, especially if broad-spectrum antibiotics have been used during the immediate postoperative period. Within a few days after operation the patient becomes ill with fever, lethargy, nausea, vomiting, abdominal distention and pain, diarrhea, and vascular collapse. The severer cases are asso-

ciated with a high mortality rate. At autopsy the intestinal mucosa is frequently found to have desquamated in the form of a pseudomembrane (148); sometimes this membrane is passed during life. In some fatal cases, however, no pseudomembrane is found (149), while staphylococci may not be found in the bowels of certain patients with pseudomembranous enterocolitis. In other patients both clostridia and staphylococci are found. A fatal case of postoperative enteritis is described below in which both clostridia and staphylococci were involved.

Postoperative staphylococcal and clostridial enteritis and peritonitis.—A 70-year-old woman underwent elective hemicolectomy for carcinoma of the cecum. Postoperatively she was treated with penicillin. Two days later she was nauseated, vomited, and began to have mucous, nonbloody diarrhea. Temperature rose to 101.8 F. on the third postoperative day but other vital signs were normal. The next morning saw some improvement in the diarrhea but her temperature was 101.2 F., pulse rate 100 and blood pressure 50 mm. systolic; serum carbon dioxide-combining power was 17 mEq./L., potassium 3.5, chloride 97, sodium 138 mg./100 ml. Later that day she went into shock, with neither pulse rate nor blood pressure measurable; at the same time she became anuric. Although clostridia and gram-positive cocci comprised most of the fecal flora, subsidence of the diarrhea led to the erroneous belief that the circulatory and renal disturbance was due to fluid and electrolyte depletion and not infection. Accordingly vasopressors and antibiotics were withheld in favor of fluid replacement therapy for the next 24 hours, but the patient continued in shock. It then became apparent that the shock was on an infectious basis and intravenous therapy with penicillin, erythromycin and levarterenol was begun. The patient did not respond to these measures and died on the fifth postoperative day, the fourth day of her enteric infection. Blood culture was sterile. Stool culture contained both coagulase-positive Staph. aureus and Cl. perfringens. Autopsy revealed generalized peritonitis due to both of these organisms. Special microscopic studies of the anastomotic site showed only superficial mucosal invasion by bacteria; there was no ulceration or pseudomembrane.

While the nature of the altered flora in this case is easily explained on the basis of antibiotic therapy, the anatomic changes in the intestine did not seem sufficiently extensive for the establishment of a clostridial infection. The possibility exists that the staphylococcus was responsible for the entire illness.

This case also emphasizes the fact that the absence of overt

diarrhea does not rule out the possibility of a continuously active enteritis, and that ileus secondary to peritonitis may lead to the sequestration of large amounts of fluid in an adynamic intestine.

Aside from the effects of the toxins of bacteria producing peritonitis, shock in this disorder can be attributed principally to the exudation of large volumes of fluid (150) and possibly also to the direct action of the inflammatory exudate on the peritoneal blood vessels and splanchnic sympathetic nerves.

Shock in Streptococcal Infections

Streptococcal infections severe enough to cause shock are relatively infrequent nowadays because their treatment with penicillin is generally satisfactory. No streptococcal infections were included in 38 cases of bacteremic shock reported by Ezzo and Knight (6). However, the series of Hall and Gold (5) included one patient with a streptococcal abscess of the thigh and one with acute streptococcal endocarditis. A recent report by Black and co-workers (85) re-emphasizes severe streptococcal infections. One patient, a 46-year-old woman, developed streptococcal septicemia with shock from paronychia; beta hemolytic streptococcus was cultured from the blood. Another patient, a 64-year-old woman, went into shock from streptococcal infection of a surgical wound. Both cases were fatal.

Streptococcal cellulitis probably caused by intramuscular injection led to shock and death in the patient described below.

Shock due to streptococcal cellulitis.—A 53-year-old man underwent a radical neck dissection for squamous cell carcinoma of the side of the neck. Postoperatively he received several intramuscular injections of analgesics but no antibiotics. On the fourth postoperative day his temperature was 102.4 F.; the fever was attributed to either wound infection or atelectasis. On the following day the temperature reached 104 F. and the patient was irrational. Chloramphenicol therapy was started, but on the sixth postoperative day the blood pressure fell to 70/50, temperature remained high, and a large area of cellulitis was noted covering the left buttock and upper thigh. Despite therapy with massive doses of penicillin, erythromycin, hydrocortisone, blood and levarterenol, the patient died in shock that day. Group A beta hemolytic streptococcus was cultured from the area of cellulitis.

In view of the experimental work relating sudden death in

animals to the cardiotoxic effects of streptolysin O (90), the following case of streptococcal shock associated with cardiac arrhythmia is of special interest.

Shock in streptococcal peritonitis.—A 49-year-old diabetic woman underwent elective cholecystectomy for chronic cholecystitis and cholelithiasis; appendectomy was performed at the same time. Her immediate postoperative condition was satisfactory. Approximately 36 hours postoperatively the temperature rose to 103.8 F., pulse to 120. Alcohol sponging helped to reduce the temperature to 100.2 F., but no antibiotics were used; at this time she felt well. Approximately 24 hours after the first temperature elevation she was found to be cool and clammy, temperature 103.5 F., pulse rate 120. The abdomen was distended. The temperature rose to 105 F. four hours later, with pulse rate 150, blood pressure 120/80. A nasogastric tube was inserted in an attempt to relieve the abdominal distention. Suddenly the patient became apprehensive, temperature reached 107.8 F., pulse rate increased to 200–250, and blood pressure fell to 80 mm. systolic. She was packed in ice, and blood transfusion and levarterenol were given, leading to a fall in temperature to 102 F. but little change in the blood pressure. Injection of lanatoside C intravenously slowed the pulse rate to 48, but shock persisted and the patient died. Penicillin and chloramphenicol were given a few hours before death without influencing the course. Autopsy revealed acute fibropurulent peritonitis due to group A streptococci; the postmortem blood culture was sterile.

Shock in Influenza

It has been pointed out that anoxia, myocarditis and a direct vascular effect of the virus or its toxin may all contribute to the development of vascular collapse in influenza. The difficulty in unraveling the immediate cause of shock is well illustrated in a case reported by Finland and associates (151). The patient, a 34-year-old woman, became ill with fatigue, malaise, cough and fever to 103.4 F. Pneumonia was noted at the right base and was accompanied by leukocytosis but negative sputum cultures. Hypotension and shock developed; signs of right basal pneumonia progressed, but no cardiomegaly, cervical venous distention or hepatomegaly was noted. The patient died after the development of complete atrioventricular block and QRS changes compatible with extreme myocardial damage. At autopsy, the lungs were crepitant throughout except at the bases posteriorly.

Marked inflammatory changes were limited to focal areas. There were degenerative and inflammatory changes in the myocardium but only slight dilatation of the heart chambers. Influenza A virus was recovered from the lung, but bacteriologic culture was sterile.

Anoxia was discounted in this patient because the pulmonary involvement was not extensive. Severe myocarditis no doubt contributed to circulatory failure, but the absence of marked cardiomegaly or elevated central venous pressure suggests that peripheral pooling took place. Thus two mechanisms may have been operative in the pathogenesis of shock.

Shock in Disseminated Candidiasis

The presence of endotoxins in fungi has been experimentally demonstrated (124), but their role in human infections is not clear. A case of shock in moniliasis (candidiasis) in which this mechanism seemed likely was reported by Braude and Rock (118). A 55-year-old man was treated with streptomycin and tetracycline for an infected abdominal incisional wound from which pseudomonas and enterococcus had been cultured. Ten days postoperatively there was a rise in temperature and the patient became stuporous; blood culture on the following day revealed a heavy growth of Candida albicans. Hemodialysis performed for progressive uremia resulted in a moderate decrease in concentration of the blood urea nitrogen. Therapy was begun with hydroxystilbamidine, but four hours later the patient went into shock. Despite blood transfusions and continuous administration of levarterenol, shock progressed and he died 24 hours later. At autopsy, both myocardium and adrenal glands contained abscesses, but the changes were not considered extensive enough to cause either cardiac or adrenal insufficiency.

Shock in other mycoses is due to specific organ failure. In disseminated histoplasmosis, adrenal involvement is frequently severe and may lead to addisonian crises within months of the original infection (152). Hypotension has also been recorded in patients with coccidioidal myocarditis (153).

Frank shock rarely develops as a direct result of heart failure in *myocarditis,* but borderline hypotension is reported frequently (128, 153–155). Shock in myocarditis more frequently results from pulmonary embolism from a right ventricular thrombus or ventricular tachycardia. In subacute bacterial endocarditis, myocarditis is less important than coronary embolism as a cause of shock (156, 157).

Cardiac tamponade is a rare complication of infection. In a bizarre case described by Jones and Tilden (10), tuberculous myocarditis led to a ruptured ventricular aneurysm. Tamponade may result from pericarditis with effusion, as illustrated by the following case of pericardial actinomycosis.

Cardiac tamponade in pericarditis.—A 57-year-old hypertensive woman developed chest pain and blood pressure fell to normal levels. Both pericardial and right pleural effusions developed and pericardial aspiration four months after onset yielded 400 ml. of blood-tinged fluid. One month later pericardial effusion had reaccumulated despite antituberculosis therapy. On hospitalization, pulse rate was 92 and blood pressure 130/100, neck veins were distended, and hepatomegaly and ascites were present. Pericardiocentesis yielded 700 cc. That evening she was found in shock without palpable pulse or measurable blood pressure. Levarterenol was given, and two further aspirations yielded a total of 1,550 ml. of fluid, resulting in stabilization of the blood pressure without the use of vasoconstricting agents. The next morning a marked pulsus paradoxicus was again noted but aspiration was not performed. Levarterenol raised the blood pressure to 110/80, but by the next morning the pressure could not be maintained above 90 systolic until aspiration was done. Thereafter, for 11 days her blood pressure was maintained by vasoconstricting drugs only, although there was no decrease in heart size; at the end of this period a pericardial window was constructed and 800–1,000 ml. fluid removed. She no longer required vasoconstrictors and was discharged nine days postoperatively. Actinomyces bovis was cultured from the pericardial tissue but not the fluid, and therapy was begun with tetracycline. Eventually the recurrent chest pain and pleural effusion disappeared and her cardiac status remained improved.

This unusual case illustrates that in cardiogenic shock from massive pericardial effusion, blood pressure can be maintained by vasoconstrictors for long periods.

Other Causes of Shock in Infections

Occasionally shock from other causes occurs during infection or is mistaken for infectious shock. Two examples follow.

Anaphylactic reaction to penicillin.—A 64-year-old diabetic man had had symptoms of prostatism for 1½ years. For three weeks before hospitalization his symptoms were aggravated and accompanied by dysuria and pain in the left testis. Eight days before admission prostatic massage was performed in the outpatient clinic and this was followed within three hours by chills and fever; chills occurred during the ensuing week. On the day of admission he was acutely ill with temperature 104 F., pulse rate 100, blood pressure 140/90, respirations 44. The prostate was moderately enlarged and exquisitely tender, and a hydrocele was present on the left. White blood cell count was 36,200, blood sugar 365 mg./100 ml., urine sugar 3 plus, acetone trace. Urine culture showed a heavy growth of E. coli. The patient was given insulin intravenously and subcutaneously, and antibiotic therapy was begun with intravenous administration of penicillin. Forty seconds after penicillin was begun, acute bronchospasm, cyanosis and shock appeared and finally cardiac arrest. These were refractory to intravenous and intracardiac administration of epinephrine, calcium gluconate and cardiac massage.

This patient was treated on an emergency basis with the diagnosis of acute prostatitis and recurring bacteremia. He was killed by anaphylactic shock.

Drug hypersensitivity mistaken for infectious shock.—A 22-year-old student was admitted in stupor and with fiery-red skin. He was febrile and after admission blood pressure fell from 110/80 to 90/60. Therapy for gram-negative septicemia was immediately begun, but both capillary smears and blood cultures were negative. Within 10 hours normotension returned. It was then learned that the patient had taken meprobamate before becoming ill.

The flushed appearance of this patient together with fever and hypotension strongly suggested infectious shock. This reaction to meprobamate has been described by Nevins (158).

TREATMENT

The aims of treatment in infectious shock are to control the infection and to correct the circulatory disturbance. On the basis of the relative roles of the infecting organism and the circulatory disturbance, patients may be divided into five groups.

Group 1: Specific antibiotic treatment for the infection is available, e.g., those due to bacteria, rickettsia and some viruses. Infection and shock must be treated simultaneously.

Group 2: Specific antibiotics are available to combat the organism but not its effects, e.g., gas gangrene, diphtheria. Administration of antitoxin and surgery may be necessary.

Group 3: No specific antibiotic treatment for the infection is available, e.g., those due to most viruses, trichinella. The objective of therapy is to sustain life long enough to allow the host to control the infection.

Group 4: Specific antibiotic treatment is available but unnecessary since invasion of tissues by infecting organisms is not a significant feature of the illness, e.g., cholera, staphylococcal food poisoning.

Group 5: The potential for shock continues to exist even after the infection is under control, e.g., pulmonary embolism from myocarditis, coronary embolism from endocarditis, chronic sequelae of poliomyelitis.

When it is recalled that, in addition to the foregoing possibilities, some infections can cause shock in more than one manner, the necessity for an accurate appraisal of the situation becomes obvious.

Antibiotics

The urgency of treatment of patients in shock necessarily will modify the approach to the selection of antibiotics. However, since the object of antibiotic therapy should always be to eliminate the infection, the guiding principle here, as in less desperate situations, should be to identify the organism as soon as possible and treat it with an optimal combination of antibiotics to which it is sensitive. Unfortunately, there is almost never time to withhold treatment, so that other guides to the selection of the proper drugs must be employed. The history is often helpful in this regard. For example, a sudden temperature elevation and shock occurring in a patient with an indwelling urethral catheter is presumptive evidence of blood stream invasion by an organism originating in the urinary tract. If the results of a recent urine culture are available, one may assume that the same organism is

responsible for infection of both urine and blood. Another example of such reasoning was employed at our center in a patient with a clinical picture compatible with septicemia (159). This diabetic was treated on the night of admission with intravenous administration of erythromycin and novobiocin because a staphylococcus sensitive to these drugs had been cultured three months earlier from an amputation stump that failed to heal. Blood culture eventually revealed a heavy growth of staphylococci identical with the one formerly isolated from the stump.

Sometimes the smear from a lesion is sufficiently characteristic to allow positive identification, as in gas gangrene, meningococcal meningitis, meningococcal skin eruption and staphylococcal pseudomembranous enterocolitis. In the infrequent cases of septicemia without an obvious focus of infection, it is wise to use a combination of antibiotics that can be expected to cover most possibilities, such as penicillin, streptomycin, tetracycline and colistin.

When shock is due to mechanical factors, as in pulmonary embolism from a mural thrombus, myocardial infarction from coronary embolism in bacterial endocarditis, or addisonian crisis in tuberculosis of the adrenals, the infection itself generally demands less urgent treatment since it is not the immediate presence of the bacteria that determines the circulatory collapse.

Treatment of Shock

Specific identification of the infectious agent will often provide a good guide to the mechanism of shock and hence appropriate treatment. It must be recognized that therapy ideally suited for shock due to fluid loss may be extremely hazardous in shock due to myocardial failure and that drugs aimed at increasing vascular tone may aggravate the effects of hypovolemia. Consideration of the various possibilities is therefore essential and should be backed up with appropriate observations and tests whenever the picture is not clear.

Fluids.—The simplest and most rewarding form of circulatory collapse in terms of response to therapy is that due to dehydration. The classic example of this is cholera. The elevated specific gravity of the blood and the hematocrit quickly establish the

nature of the circulatory deficit, and prompt response is usually seen with an initial infusion of normal saline. Subsequent fluid and electrolyte administration may be guided by fecal losses (160) or by plasma specific gravity (161). Initial fluid deficits as judged by specific gravity of the plasma or blood may be several liters in patients ill for less than 12 hours, and fecal losses in severe cases may exceed 15 L. in 24 hours during the acute stage of the disease.

While dehydration is particularly profound in cholera, it also plays a prominent part in other diarrheal infections such as salmonella and shigella gastroenteritis and pseudomembranous enterocolitis, as well as staphylococcal food poisoning. In all these, therefore, the administration of electrolytes and fluid is essential.

Whole blood or plasma may be beneficial in shock due to gram-negative endotoxemia regardless of severe external fluid loss. In studies on meningococcus toxin (58), dogs under the influence of sublethal doses of endotoxin could be thrown into shock by small hemorrhages that the normal animal would tolerate easily. On the other hand, infusion of dextran raised the cardiac output appreciably. This suggests that endotoxemia increases the susceptibility to shock from fluid loss and emphasizes the importance of maintaining an adequate circulatory volume in patients.

The fluid loss in hemorrhagic fever removes plasma proteins as well as electrolytes, so that administration of human serum albumin has been helpful in treatment (162). On the other hand, fluid therapy must be given with great caution in view of the oliguric phase that generally follows, especially since the original hypovolemia represents only a redistribution of fluid into interstitial tissues and not actual loss. Vasoconstricting agents have therefore been recommended as adjuncts (163). Unfortunately, successful treatment of shock does not prevent the development of renal failure, which is the result, at least in part, of intrinsic vascular damage (164).

Vasoconstricting drugs.—A different therapeutic problem is posed by collapse due to peripheral pooling. In this situation drugs aimed at restoration of vascular tone are traditionally employed. Probably the most widely used of these is levarterenol, which is given by intravenous drip with continual monitoring of

blood pressure; unusually high concentrations are sometimes necessary. Among the many others are metaraminol, phenylephrine, mephentermine, methoxamine and ephedrine. Many theoretical considerations are involved in the choice of this group of drugs (165). Arguments against their use have been advanced, pointing out false impressions gained from blood pressure measurements (3) and the differential changes in sensitivity of arterioles and capillaries to vasoconstrictor agents during the progression of shock (166). Other undesirable side effects that have been attributed to the use of powerful vasoconstrictors are myocarditis (167) and hepatic necrosis (168). Nevertheless, most investigators agree that vasoconstrictors are indicated in this form of shock both because of the functional nature of the defect and because of the good results obtained in practice (169, 170).

Steroids.—The value of adrenocortical steroids has also been debated. The two important questions regarding their use are: *(1)* Do they interfere with host defenses so as to aggravate the underlying infection? *(2)* Do they help in the treatment of infectious shock?

The safety of the administration of corticosteroids in infectious diseases has been a disputed subject ever since the demonstration of their effects in lowering the resistance of animals to various infections (171–178). The suggestion has also been made (56) that in man adrenal steroid therapy may be related to the development of renal cortical necrosis in meningococcemia. On the other hand, general experience with human patients has shown that, in the presence of adequate antibiotic coverage, the short-term use of steroids in many infections (96, 179–181) may hasten symptomatic recovery and obviate some of the undesirable by-products of the inflammatory response, without making the infection more difficult to control.

Whether adrenocortical steroids actually help in the management of infectious shock is, however, less certain. The theoretical basis for their use includes their known hypertensive properties; the possibility that, despite a supernormal circulating steroid level during severe infection (57), the actual need for steroids in the situation at hand is not met, so that relative adrenal insufficiency exists; and the somewhat less specific concept of "buying time" to allow the host to rally his defenses before he is over-

come (182). In actual practice their value can only be estimated, and it is possible that their success may well be ascribed either to their anti-inflammatory action independent of any effect on blood pressure or to the concomitant use of other agents.

Oxygen.—The value of oxygen therapy in infectious shock depends on the demonstration of arterial unsaturation. In certain circumstances, such as influenzal pneumonia and poliomyelitis, anoxemia is a significant contributory feature. In influenza, where owing to the inflammatory exudate a diffusion barrier exists and marked changes in compliance occur ("stiff lungs") (183), the administration of oxygen by positive pressure has been recommended.

Digitalis.—The use of digitalis is indicated whenever there is reason to believe that heart failure is playing a significant role in the patient's illness. In certain cases of myocarditis, shock results directly from heart failure. Conversely, particularly in older people, shock may lead to myocardial anoxia, dangerous arrhythmias and heart failure. Acute right ventricular failure may be precipitated by pulmonary embolism. Caution is necessary, however, in giving digitalis to patients with either myocarditis or myocardial anoxia since in both instances the sensitivity of the myocardium to digitalis may be increased.

Special therapeutic problems.—Certain conditions pose unique problems in therapy. The pathology of gas gangrene has already been alluded to, and here surgery is usually necessary to remove the focus of toxin production. Hysterectomy may be necessary in puerperal or postabortal clostridial endometritis. The instillation of normal feces into the intestine has been advocated in staphylococcal pseudomembranous enterocolitis in order to establish a normal intestinal flora (184), but its value has not been established.

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